United States
Environmental Protection
Agency

IRIS Today – An Update on Progress

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American Petroleum Institute Toxicology Group
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New Leadership Structure in NCEA

- **In January 2017, EPA appointed new leadership to the National Center for Environmental Assessment and to its IRIS Program.**
  - NCEA Director: significant experience in the chemical and energy industries, and formerly the Director of ORD's Chemical Safety for Sustainability National Research Program, Tina Bahadori brings knowledge of TSCA, innovative applications of computational toxicology, and exposure science.
  - IRIS Program Director: As a recognized leader in systematic review, automation, and chemical evaluations, Kris Thayer brings experience in early partner and stakeholder engagement and input, and demonstrated actions to increase capacity and transparency in assessments.
- **Improved responsiveness and accountability through Senior Leadership Team**
- **Integrating across the spectrum of human and ecological RA practices**

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- **Created in 1985 to foster consistency in the evaluation of chemical toxicity across the Agency.**
- **IRIS assessments contribute to decisions across EPA and other health agencies**
- **Toxicity values**
  - Noncancer: Reference Doses (RfDs) and Reference Concentrations (RfCs).
  - Cancer: Oral Slope Factors (OSFs) and Inhalation Unit Risks (IURs).
- **IRIS is the only federal program to provide toxicity values for both cancer and noncancer effects.**
- **IRIS assessments have no direct regulatory impact until they are combined with**
  - Extent of exposure to people, cost of cleanup, available technology, etc.
  - Regulatory options, which are the purview of EPA's program offices.

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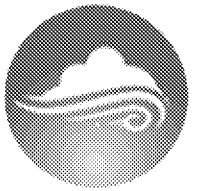
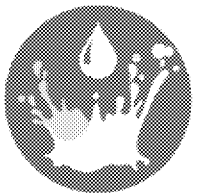
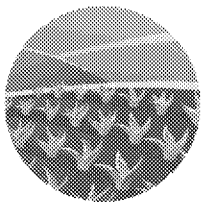
IRIS Addresses Agency Priorities and Mandates

IRIS

- Clean Air Act (CAA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)





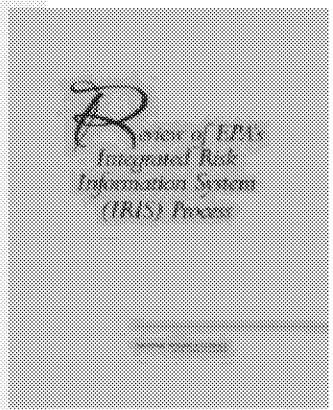


Broad Input to Support

- Agency Strategic Goals
- Children's Health, Environmental Justice

National Academy of Sciences (2014) Overarching Statements

2014



"Overall, the committee finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The NRC formaldehyde committee recognized that its suggested changes would take several years and an extensive effort by EPA staff to implement. Substantial progress, however, has been made in a short time, and the present committee's recommendations should be seen as building on the progress that EPA has already made." [p.9]

" . . . the IRIS program has moved forward steadily in planning for and implementing changes in each element of the assessment process. The committee is confident that there is an institutional commitment to completing the revisions of the process . . . Overall the committee expects that EPA will complete its planned revisions in a timely way and that the revisions will transform the IRIS Program." [p.135]

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How is IRIS Focusing?

- **Increase transparency and full implementation of systematic review**
  - implement using approaches that foster consistency across the IRIS program; many active and all new starts address ALL SR-related recommendations of 2014 NRC report
- **Modernize the IRIS Program**
  - through automation and machine learning to expedite systematic review, incorporation of emerging data types
- **Modularize product lines**
  - implement a portfolio of chemical evaluation products that optimize the application of the best available science and technology. These products will allow IRIS to remain flexible and responsive to clients within the EPA as well the diverse collection of stakeholders beyond EPA, including states, tribal nations, and other federal agencies.
- **Enhance accessibility**
  - provide outreach and training to make systematic review practices ubiquitous and more accessible; enhance data sharing through publicly available software platforms for assessments developed by EPA, other federal and state agencies, industry, academia and other third-parties.

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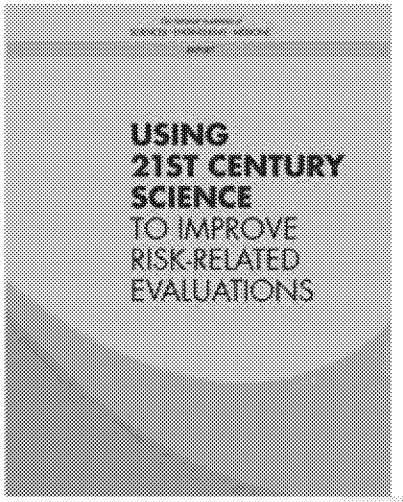
Other IRIS Improvements



Next Generation IRIS

- IRIS in the 21st Century – implement recommendations of the NAS 2017 report, Using 21st Century Science to Improve Risk-Related Evaluations;
- Collaborate with EPA's National Center for Computational Toxicology (NCCT) to build expert-judgement case studies that inform assessment development and fill gaps in assessments, especially for data poor chemicals; inform where resources should be strategically invested to generate additional data.

Improved Management Practices

- Create efficiencies – engage other agencies to share common practices, data, and tools, and more efficiently leverage resources across the federal government.
- Improve timeliness and responsiveness – deploy program and project management tools to more effectively and efficiently utilize human resources to ensure timely delivery of products.

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A Portfolio Approach

- Moving away from a 'one-size-fits-all' approach to risk assessment towards a spectrum of assessment products to meet specific decision contexts;
- facilitating the incorporation of new science into risk assessment and decision-making;
- enabling assessments to be better tailored to meet needs of decision makers;
- increasing the number of chemicals that can be evaluated for their effects on human health by utilizing constrained resources in the most efficient manner.

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IRIS Multi-Year Agenda

- **Released to the public December 2015**
  - Result of a survey EPA program and regional offices for their assessment needs balanced with resource availability.
  - Other chemicals were also carried over from earlier prioritizations
  - Reflects global priorities
- **In FY 2018, planning to launch a process to reaffirm now and again regularly these priorities, identify new or more urgent needs.**
- **Plan to engage the states in this reaffirmation.**

Group	Chemicals
1	Manganese
	Mercury/methylmercury
	Nitrate/nitrite
	Perfluoroalkyl compounds
	Vanadium and compounds
2	Acetaldehyde
	Ammonia (oral)
	Cadmium and compounds
	Uranium
3	Di-(2-ethylhexyl) phthalate
	Dichlorobenzene isomers
	Methyl t-butyl ether (MTBE)
	Nickel and compounds
	Styrene

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Broader Engagement

- **SAB Briefing, August 30, 2017**
  - **SAB letter to the Administrator about IRIS:** https://yosemite.epa.gov/sab/sabproduct.nsf/0/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf
  - "The SAB has observed significant enhancements in the IRIS program over the past few years, with impactful changes over the past year, and marked progress over the past six months. "
  - "The changes are so extensive and positive that they constitute a virtual reinvention of IRIS. "
  - "The SAB notes that no other federal entity performs the IRIS functions, and that IRIS helps ensure consistency in chemical assessments within the Agency and across the federal government. "
- **SAB Chemical Assessment Advisory Committee (SAB -CAAC) briefing, September 27-28, 2017**
- **NAS Agreements**
  - **Peer review formaldehyde (Congressional requirement)**
  - **A public meeting to evaluate IRIS's progress and to issue a consensus report within 6 months of that meeting.**
- **Stakeholder outreach**
  - **Systematic review communities**

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Operationalizing Systematic Review

Guidance to Assist Interested Persons

in Developing and Submitting

Draft Risk Evaluations

Under the

Toxic Substances Control Act

June 2017

Prepublication Copy Notice:

The EPA Administrator signed the following *Federal Register* document on June 22, 2017:

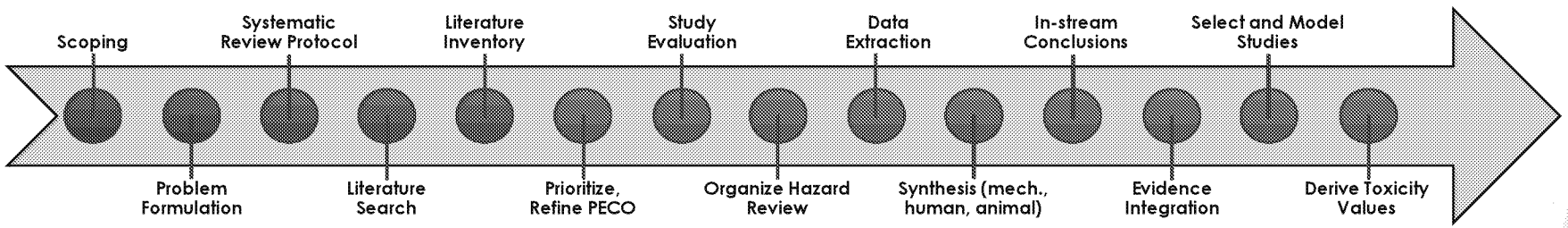
Title: **Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act**

Action: Final Rule

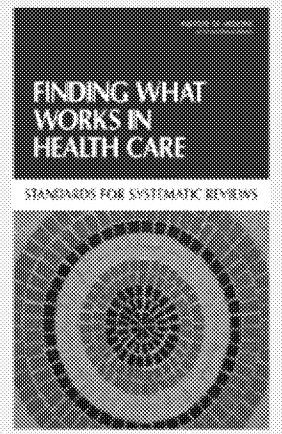
FRL: 9964-38

Docket No.: **EPA-HQ-OPPT-2016-0654**

This is a **prepublication version** of the document that EPA is submitting for publication in the *Federal Register*. While the Agency has taken steps to ensure the accuracy of this prepublication version of the document, **it is not the official version** of the document for purposes of public comment or judicial review. Please refer to the official version of the document that will appear in a forthcoming *Federal Register* publication



Systematic Review



A structured and documented process for transparent literature review[1,2]

"… systematic review is a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. The goal of systematic review methods is to ensure that the review is complete, unbiased, reproducible, and transparent"

[1] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act. EPA-HQ-OPPT-2016-0654. https://www.epa.gov/sites/production/files/2017-06/documents/prepubcopy_tsca_riskeval_final_rule_2017-06-22.pdf

[2] Institute of Medicine. Finding What works in Health Care: Standards for Systematic Reviews. p.13-34. The National Academies Press. Washington, D.C. 2011

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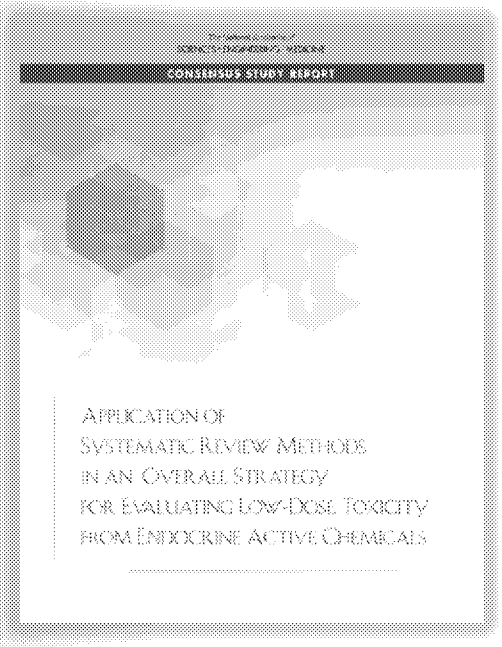
NAS (2017): Reflections and Lessons Learned from the Systematic Review



"….one disadvantage in conducting a systematic review is that it can be time and resource intensive, particularly for individuals that have not previously conducted a systematic review." [p.157]

"The committee discussed at length whether it could provide EPA with advice about when a systematic review should be performed but decided it could not be more specific because that decision will depend on the availability of data and resources, the anticipated actions, the time frame for decision making, and other factors." [p.157]

"The committee also recognized that it might be advantageous for EPA to build on existing systematic reviews that are published in the peer-reviewed literature." [p.157]

"The committee recognizes that the methods and role of systematic review and meta-analysis in toxicology are evolving rapidly and EPA will need to stay abreast of these developments, strive for transparency, and use appropriate methods to address its questions." [p.157]

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Making Systematic Review (SR) Pragmatic and Feasible For IRIS

- Standard operating procedures (IRIS Handbook), templates (draft assessment plans, chemical-specific protocols), and regular training
- Solicit early feedback during scoping and problem formulation via assessment plans
- Utilize iterative protocols to ensure communication on included studies and focus on best-available and most-informative evidence as the assessment progresses
- Multiple assessment products ("modularity")
- Targeted focus, especially for evidencerich topics
  - Make better use of existing assessments as starting point
- Use of specialized SR software applications/automation and project management tools

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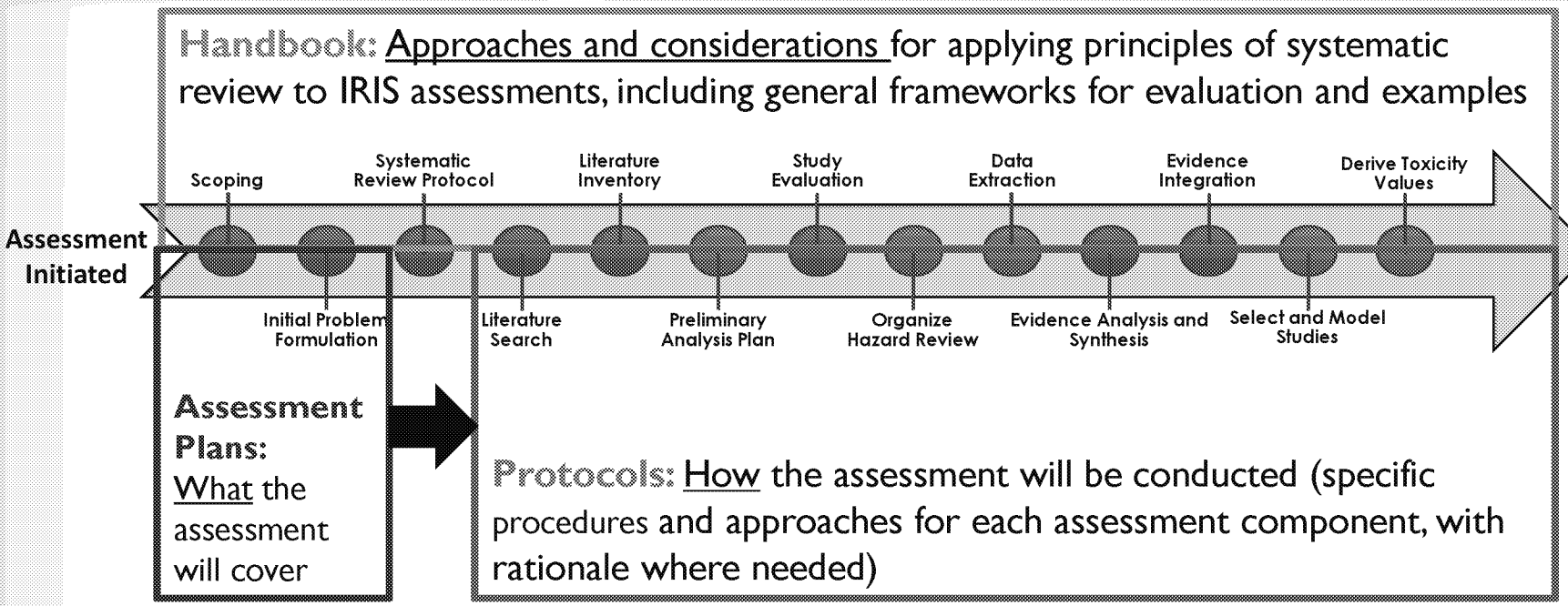
Standard Operating Procedures (SOPs), Templates & Training



- **Promote consistency across the IRIS Program, which is implemented across staff in different Divisions and geographic regions**
- **Assemble systematic review support teams: One for handbook/template protocol and another to provide support to chemical assessment teams (e.g., screening, study evaluation, data extraction, use of specialized software, etc.)**
- **Provide regular training via skill-building seminars, focused discussions, and retreats**

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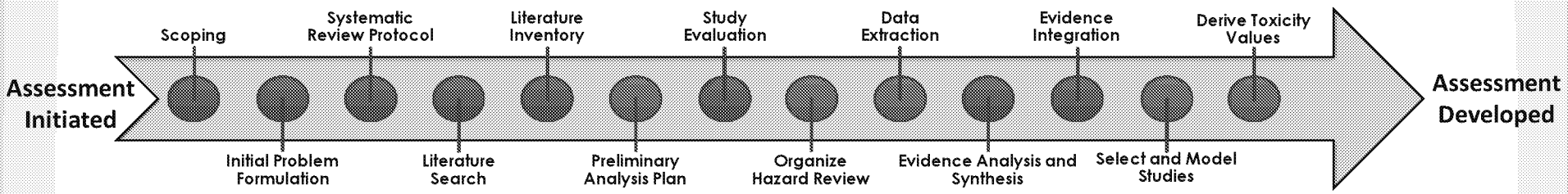
IRIS Handbook



- **Level of detail aimed for EPA staff and contractors, e.g., use of HERO**
- **Currently being updated to reflect agency input and evolving IRIS practices to implement SR**
  - **Anticipate public posting in 2018**
- **Evergreen to reflect future advances in implementing SR**
- **Chemical-specific protocols are stand-alone method description documents and do not rely on IRIS Handbook to convey methodology**

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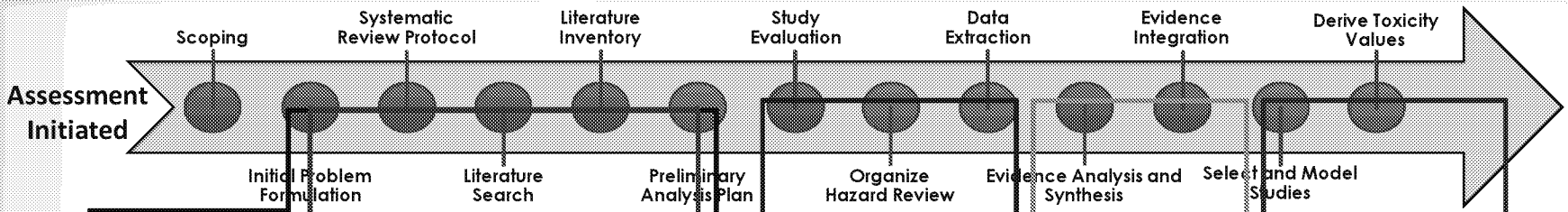
Systematic Review Tools



HERO
Literature searching, storage and documentation (tagging)

SWIFT Review
Problem formulation

SWIFT Review
DoCTOR
Machine learning for screening prioritization

Distiller
SWIFT Active
Multiple reviewer reference screening and tracking (HERO-tagging)

HAWC
DRAGON
Modules to track multiple reviewer study evaluations

Extracted data storage

HAWC
Interactive graphical display, evidence profile tables

GRADEPro
Evidence profile table, evidence to decision making

METAXL, Metafor
Evaluation of heterogeneity or combined study results analysis

Database of SR software tools:
http://systematicreviewtools.com/

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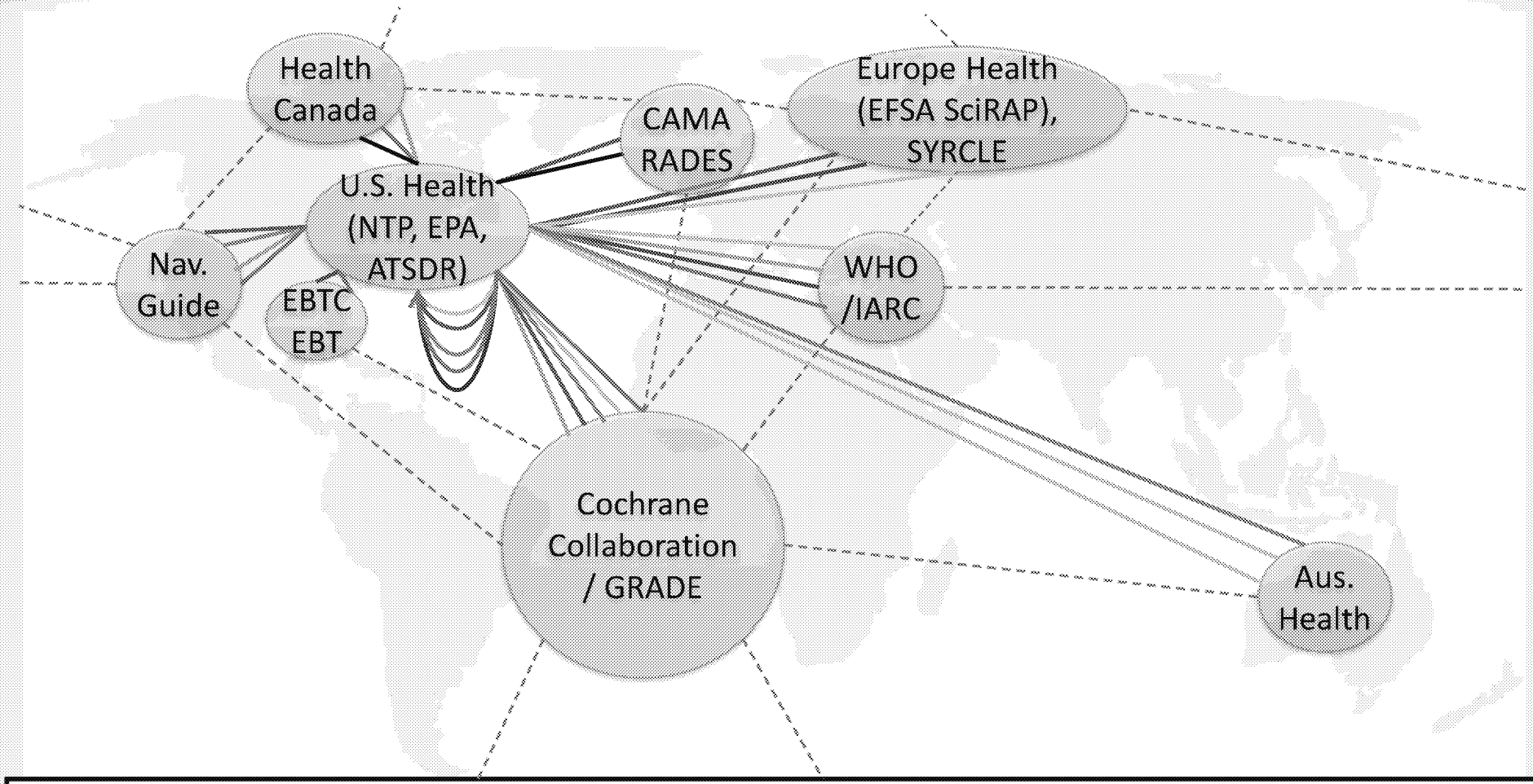
Systematic Review Collaborations in Environmental Health



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IRIS Assessment Plans and their Role within the IRIS Process

Backup Slides

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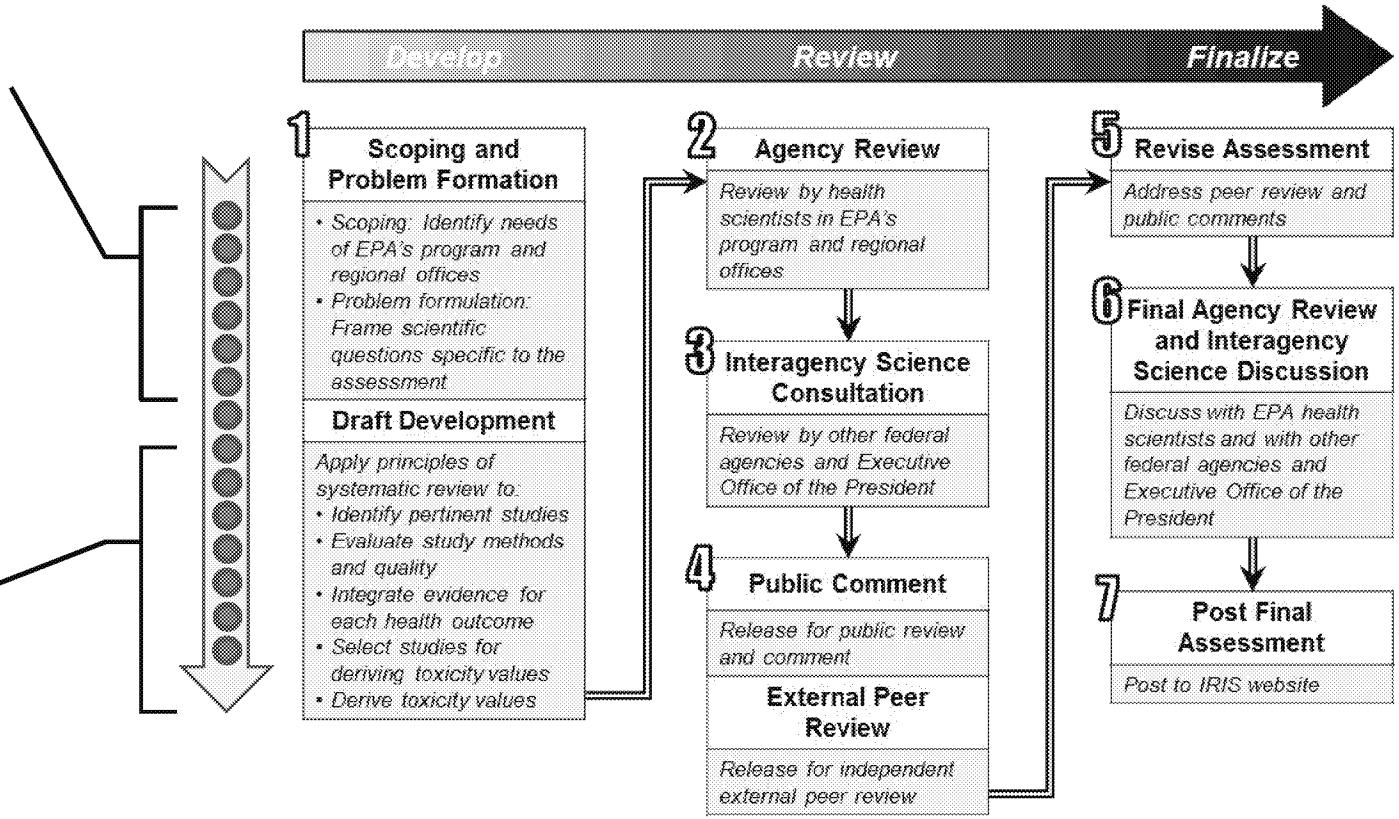
IRIS Assessment Plans in the 7-Step IRIS Process

IRIS Assessment Plans (IAPs)

- What the assessment will cover

Systematic Review Protocols

- How the assessment will be conducted



https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process

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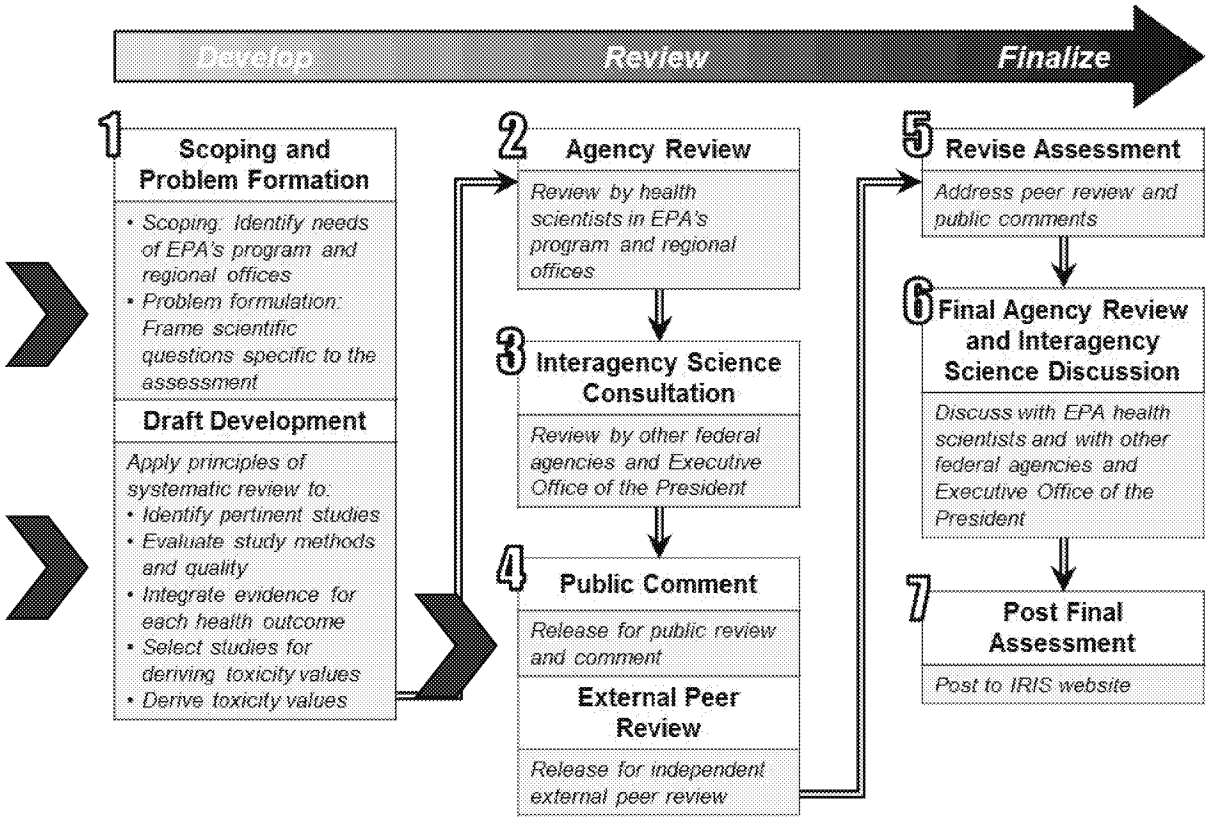
Transparency in the IRIS Assessment Process

Assessment materials will be made available for public comment at various stages in development

- **Early Step 1: IRIS Assessment Plans (IAPs)**
  - The federal docket for public comment is open for 30 days
- **Mid-Step 1: Systematic Review Protocols**
- **Step 4: Public Comment Assessment Draft**



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IAPs Represent Continuous Refinement of Scoping/Problem Formulation Materials

07/2014 Ethylbenzene Scoping & Problem Formulation Document	09/2017 Ethylbenzene Assessment Plan Document
Introduction and background	Introduction and background
Production and use, human exposure pathways, environmental fate	Concise discussion to extent this information provides necessary context
Scoping ("Scope of the Assessment")	Scoping ("Scoping Summary")
[Not explicitly discussed]	Table of Agency Interest
Problem Formulation	Problem Formulation
Preliminary Literature Survey (conducted by manual review of studies retrieved)	Preliminary Literature Survey (conducted using various approaches, e.g. machine-learning, prior assessments)
Systematic Review Elements	Systematic Review Elements
[Not explicitly discussed]	Specific Aims
Hazard Questions for Systematic Review	Draft Populations, Exposures, Comparators, Outcomes (PECO)
[Not explicitly discussed]	Assessment Approach
Key Issues	Key Science Issues

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What IAPs Are Intended to Be

IAPs are <u>what</u> will be covered in the assessment, including:

- **Summary of the assessment plan:**
  - Scoping and initial problem formulation determinations
  - Overall objectives and Specific aims
- **Presentation of draft PECO (Populations, Exposures, Comparators, and Outcomes)**
  - Outline what evidence will be considered most pertinent
- **Discussion of the fit-for-purpose approach:**
  - Address the need and decision context (e.g., targeted to outcome, route, and/or modular)
- **Identification of key areas of scientific complexity**

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What IAPs Are Not Intended to Be

IAPs are not intended to be a discussion of how the work will be conducted.

Because they represent a very early step in the systematic review process, IAPs will not include detailed review of various topics, including:

- Agent use or production
- Agent properties, stability, biochemistry, metabolism, prevalence or fate
- Quality of identified literature
- Extensive discussion on hypothesized mechanisms or modes of human toxicity
- Strength or direction of reported hazard associations
- Other science issues

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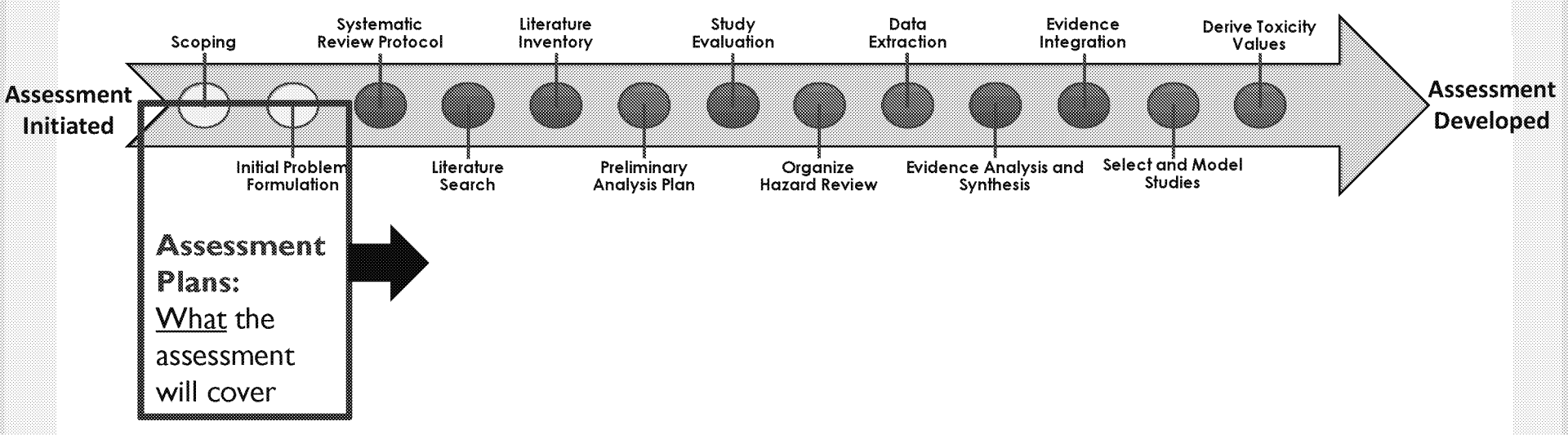
IAP Purpose



As the INITIAL step in problem formulation, IAPs summarize:

- Scoping and initial problem formulation conclusions
- Objectives and specific aims
- Draft PECO (Populations, Exposures, Comparators, and Outcomes)
- Identification of key areas of scientific complexity

Draft IAPs Presented as Case Studies

- **Chloroform**
  - RfD, cancer assessment and mode-of-action (MOA) (from 2001); IUR (from 1987)
  - Focusing on inhalation exposure – will attempt to derive a noncancer RfC based upon inhalation data, and conduct a cancer assessment
- **Nitrates/Nitrites (NO_3^-/NO_2^-)**
  - RfDs (from 1991, 1987)
  - Focusing on oral exposure – will attempt to derive separate noncancer RfDs for NO_3^- and NO_2^-, and conduct a cancer assessment
- **Ethylbenzene**
  - RfC and RfD (from 1991, 1987), cancer assessment (from 1988)
  - Modular approach – due to different levels-of-effort needed, may derive noncancer RfC, RfD, and a cancer assessment, separately and sequentially

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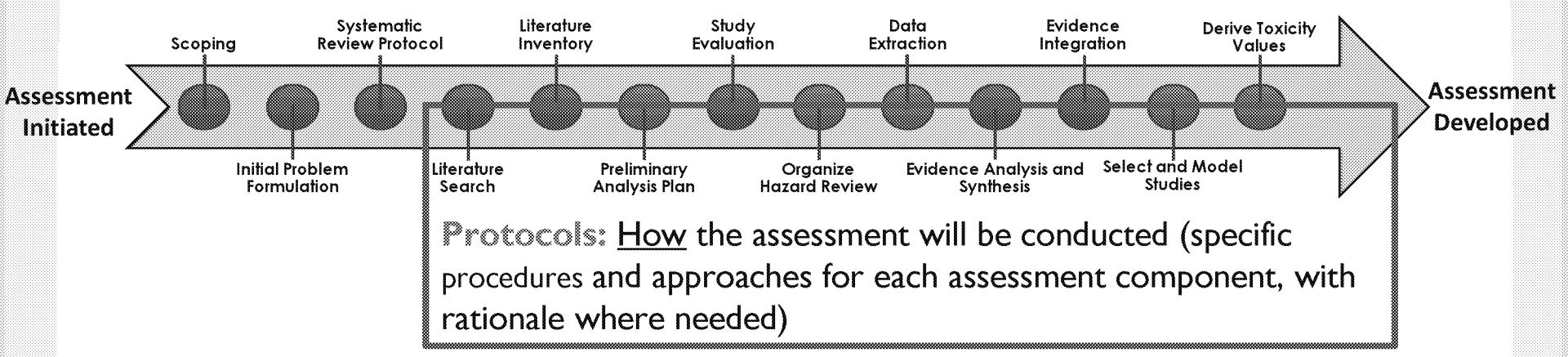
Protocol Release



- **Post protocol for public shortly after review of IAP**
- **Protocol captures changes made to IAP in response to public science meeting discussions**
- **Protocol is a separate document from draft assessment (supplemental material document, ~40-60 pages)**
- **Protocol is iterative to ensure the SR focuses on the best available and most informative evidence**
  - **Protocols include revision history to reflect updates**

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